



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/581,045	05/30/2006	Masami Takahashi	TAKAHASHI38	7118

1444 7590 06/26/2007
BROWDY AND NEIMARK, P.L.L.C.
624 NINTH STREET, NW
SUITE 300
WASHINGTON, DC 20001-5303

EXAMINER

CHANDRAKUMAR, NIZAL S

ART UNIT	PAPER NUMBER
----------	--------------

1625

MAIL DATE	DELIVERY MODE
-----------	---------------

06/26/2007

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/581,045

Applicant(s)

TAKAHASHI ET AL.

Examiner

Nizal S. Chandrakumar

Art Unit

1625

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 07 June 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-10 is/are pending in the application.
- 4a) Of the above claim(s) 9 and 10 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-8 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

This application filed 05/30/2006 is a 371 of PCT/JP04/17543 11/26/2004. Claims 1-10 are pending.

Election/Restrictions

Applicant's election with traverse of group 1 claims 1-8 in the reply filed on 06/07/2007 is acknowledged. The traversal is on the ground(s) that the reference cited in the restriction does not read on the claims of the application. This argument is not relevant because, the reference cited in restriction is not for art rejections under USC 103 or USC 102, rather the reference was cited in support of Restriction requirement under 35 U.S.C. 121 and 372.

Applicant's arguments regarding the patentably distinct and non-obvious nature of the groups is not relevant at this point. At the point when the base compound claims become allowable, the rejoining of the process claims will be evaluated.

The requirement is still deemed proper and is therefore made FINAL.

Claim Rejections - 35 USC § 103

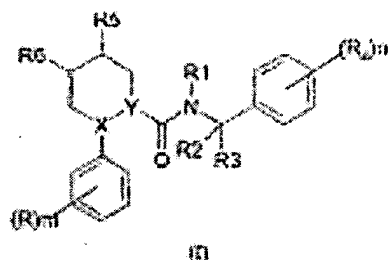
1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Art Unit: 1625

Claims 1 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Alvaro et al. (WO 03/066589 A1).

Alvaro et al. teach (page 1 lines 19 –36 in particular line 36, page 2 lines 38-40, page 3 lines 1-5) compounds of the formula I wherein R2 and R3 are independently hydrogen or C1-4 alkyl.



4. Alvaro et al. does not teach compounds wherein R2 and R3 both are alkyl as instantly claimed.
5. Though Alvaro et al. does not actually make the dialkyl (R2 and R3 both alkyl) compounds but generically claims such modifications, It would have been obvious to someone of ordinary skill in the art of medicinal chemistry to replace hydrogens with lower alkyl groups with a reasonable expectation of success because it is well known in the art that such smaller changes could provide compounds with improved properties.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 1-8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a few compounds of the formula I, does not reasonably provide enablement for the wide variety of structures encompassed by the formula I. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The specification enables the preparation of compounds of the formula I wherein $Z = N$, $R_{4a} = R_{4b} = R_3 = CH_3$ and $R_3 = R_2 = H$. The specification is not enabling for the preparation of compounds of the formula wherein $Z = O$. The specification is not enabling for compounds wherein R_2 is other than hydrogen. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The determination that "undue experimentation" would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the relevant factual considerations. Enablement is considered in view of the Wands factors (MPEP 2164.01 (a)). These include: breadth of the claims; nature of the invention; state of the prior art; amount of direction provided by the inventor; the level of predictability in the art; the existence of working examples; quantity of experimentation needed to make or use the invention based on the content of the disclosure; and relative skill in the art. All of the factors have been considered with regard to the claim, with the most relevant factors discussed below.

1) The nature of the invention: The claims are drawn to N-acyl-2-phenyl piperidines, with the intended use of these compounds in antagonizing tachykinin receptor.

2) The level of skill in the art: The skill of one of ordinary skill in the art is very high, e.g., Ph.D. and M.D. level technology.

3) The state of the prior art: The state of the prior art and its predictability or lack thereof limit whether one could prepare the compounds of formula I with all the claimed variables. With regards to the variable $Z=O$, while primary alcohol could form carbamates easily, this is not the case wherein sterically demanding tertiary alcohols are involved. Note that the limitation that both $R4a = R4b$ are alkyl makes the alcohol tertiary and bulky. In addition, given the amine part of the carbamate is fairly crowded because of the presence of the 2-aryl substitution, the success of formation of carbamate, at the minimum, is unpredictable. It is not surprising that there is no Example of a carbamate present in the specification (vide infra). Thus undue experimentation would have been needed to make and use the claimed inventions of carbamates. With regards, to the $R2$ substitutions claimed, it is unpredictable as to the compatibility of the pyridinium intermediate [IX] for reaction with Grignard reagents [X] when $R2$ is other than hydrogen (page 44 of the specification). For instance the survivability of $R2=halogen$ in this reaction as well as the subsequent reduction of the double bond is unpredictable. It is not surprising that there is no Example present in the specification for a compound with $R2$ other than hydrogen (vide infra).

4) The amount of direction or guidance present: The specification contains guidance for making of compounds of the formula I wherein $Z = N$, $R_{4a} = R_{4b} = R_3 = CH_3$ and $R_3 = R_2 = H$.

The specification cites a prior art reference as guidance for assessing the ability of the compounds in antagonizing tachykinin receptor. It is not seen where the biochemical data, IC_{50} or EC_{50} or ED_{50} information, is present in the specification.

6) The presence or absence of working examples. With regards to R_2 and Z variables of the formula I, working examples present in the specification are limited to making compounds of the formula I wherein $Z = N$, $R_{4a} = R_{4b} = R_3 = CH_3$ and $R_3 = R_2 = H$.

7) The breadth of the claims: Claimed compounds of formula I include generically claimed substituents on all the substitutable positions in the core structure of the formula I, making the breadth of the claims large

8) The quantity of experimentation needed: In the instant case, there is a substantial gap between the compounds demonstrated and the breadth of the claims. Given the direction and working Examples provided in the specification, in order to utilize the invention as claimed, the skilled artisan would be presented with an unpredictable amount of experimentation. It is the Examiner's position that the chemistry enabled for the preparation of $R_2 = H$ is not extendable for making all the groups claimed for this variable. It is also the Examiner's position that the applicant did not have possession of a carbamate conforming to the formula I at the time of the instant application. In addition, the chemistry for described for N-methylation (R_{12})

would be questionable for the generic concept of R12 being alkyl. Consequently, a burdensome amount of research would be required by one of ordinary skill in the art to bridge this gap. The instant disclosure is broad and generic.

The instant compounds are claimed to be antagonists of tachykinin receptor. No data is present, but a statement is present in the specification as to the potency being excellent [0001]. It is well known in the art that in vitro activity is not necessarily a predictor of in vivo efficacy. There is no teaching in the specification or working examples to show how the instant compounds would have utility in treating diseases in which tachykinin receptor antagonism or inhibition is implicated. Therefore it would be difficult to predict what compounds within the broad genus of formula I with wide possibilities for substituents for R1, R2, 4a and 4b or substituents on the aromatic ring would possess the desired activity, thus creating an extraordinary amount of trial and error experimentation to identify a N-acyl-2-phenyl piperidine derivative with desirable biological property.

The specification is enabling for making N-acyl-2-phenyl piperidines of formula I wherein Z = N (CH3), R4a = R4b = R3=CH3, R2=H.

Allowable Subject Matter

Claims 2-7 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

The following is a statement of reasons for the indication of allowable subject matter: The closest prior art is taught by Alvaro et al. (WO 03/066589 A1). However there is no teaching or suggestion in the prior art (see under 102-b rejection) as to the substituent R1 of the instant case.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nizal S. Chandrakumar whose telephone number is 517-272-6202. The examiner can normally be reached on 8.30 am – 5 pm Monday-Friday.

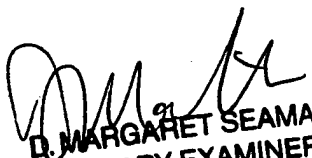
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached at 571-272-0867 or Primary Examiner D. Margaret Seaman can be reached at 571-272-0694. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only.

Art Unit: 1625

For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000


Nizal S. Chandrakumar


D. MARGARET SEAMAN
PRIMARY EXAMINER

DETAILED ACTION

This application filed 05/30/2006 is a 371 of PCT/JP04/17543 11/26/2004. Claims 1-10 are before the Examiner and subject to the following Election/restrictions.

Election/Restrictions

1. Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions, which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

Group 1, claim(s) 1-8 are, drawn to N-acyl derivatives of 2-phenylpiperidines.

Group 2, claim(s) 9-10 are, drawn to process of making N-acyl derivatives of 2-phenylpiperidines.

The inventions listed as Groups 1-2 do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: the common technical feature in all groups is N-acyl derivatives of 2-phenylpiperidines. This element cannot be a special technical feature under PCT Rule 13.2 because the element is shown in the prior art, see WO 03/066589, page 3.

Because these inventions are independent or distinct for the reasons given above and there would be a serious burden on the examiner if restriction were not required; because the inventions require a different field of search (see MPEP § 808.02), restriction for examination purposes as indicated is proper.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species or invention to be examined even though the requirement be traversed (37 CFR 1.143) and (ii) identification of the claims encompassing the elected invention.

The election of an invention or species may be made with or without traverse. To reserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the restriction requirement, the election shall be treated as an election without traverse.

Should applicant traverse on the ground that the inventions or species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the inventions or species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i). Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nizal S. Chandrakumar whose telephone number is 571-272-6202. The examiner can normally be reached on 8.30 am – 5 pm Monday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thomas McKenzie can be reached on 571-272-0670 or Primary Examiner D. Margaret Seaman can be reached at 571-272-0694. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO


Application/Control Number: 10/581,045

Page 5

Art Unit: 1625

Customer Service Representative or access to the automated information system, call
800-786-9199 (IN USA OR CANADA) or 571-272-1000.


Nizal S. Chandrakumar


D. MARGARET SEAMAN
PRIMARY EXAMINER